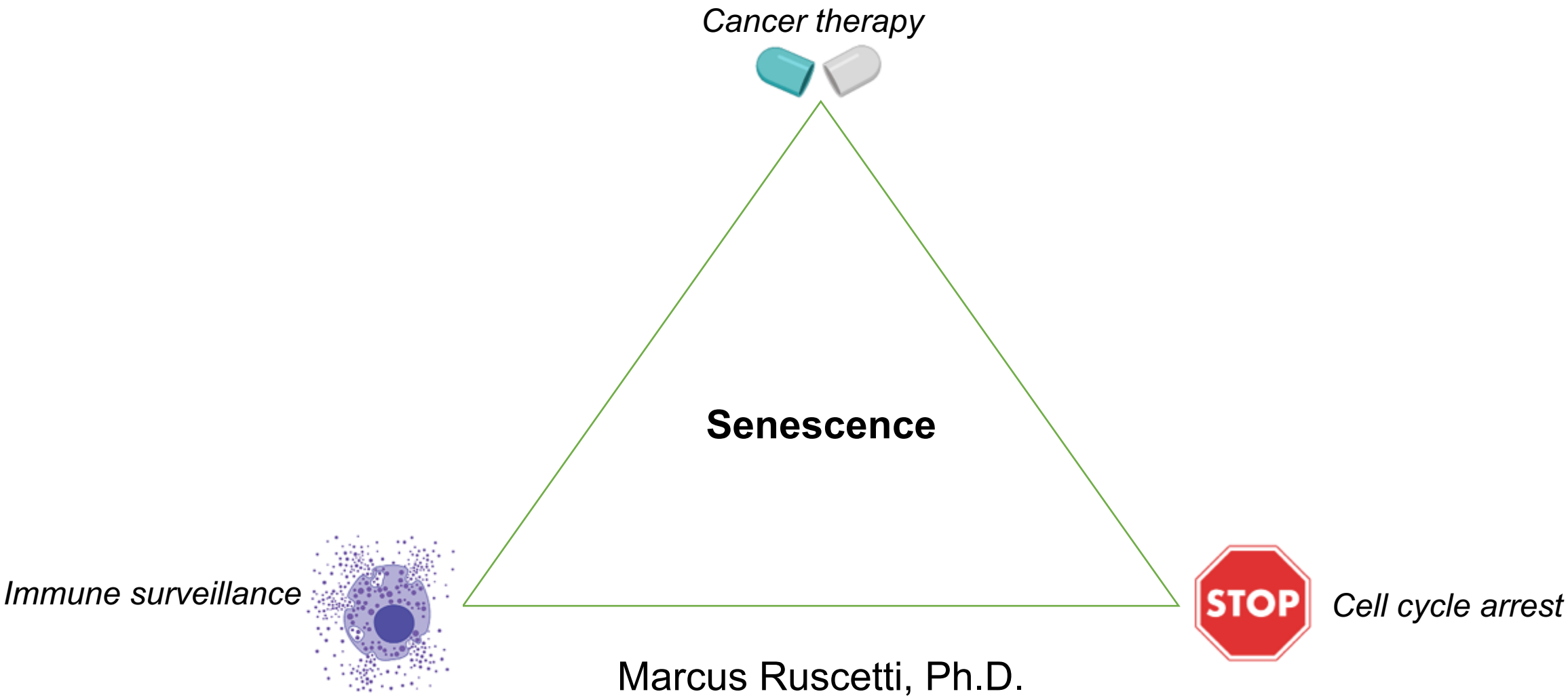
2020-10-26

# Harnessing Cellular Senescence for Cancer Immunotherapy

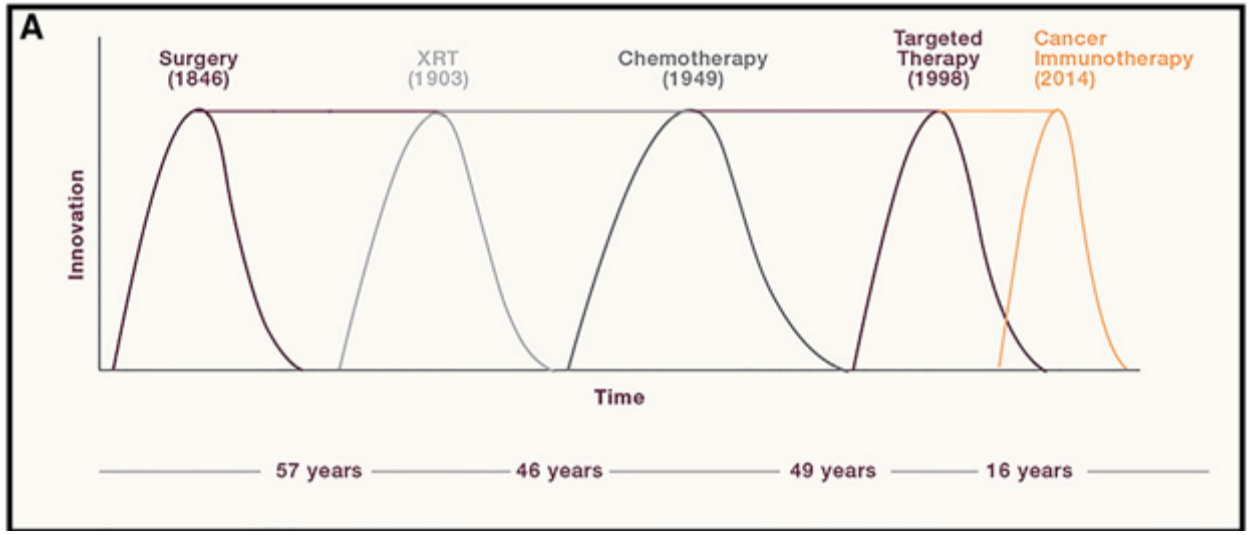
Marcus Ruscetti
*University of Massachusetts Medical School*

# Harnessing Cellular Senescence for Cancer Immunotherapy

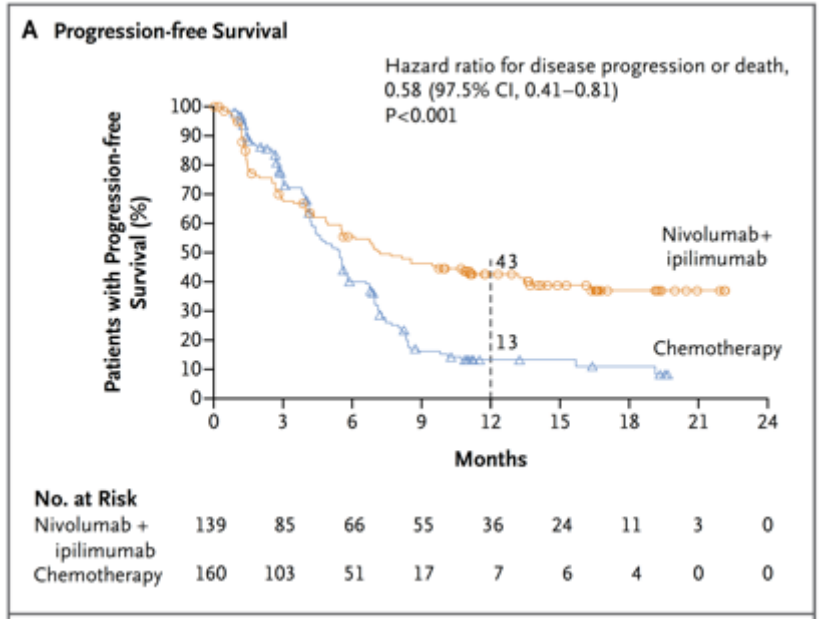



Marcus Ruscetti, Ph.D.
Assistant Professor
Molecular Cell and Cancer Biology
UMass Medical School
10-26-20

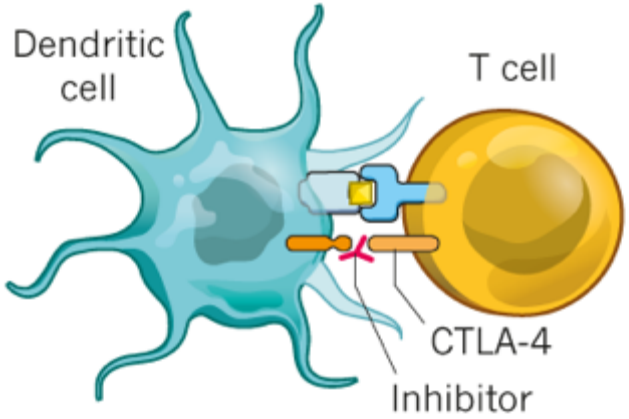
# Immune Checkpoint Blockade has revolutionized treatment landscape of many cancers

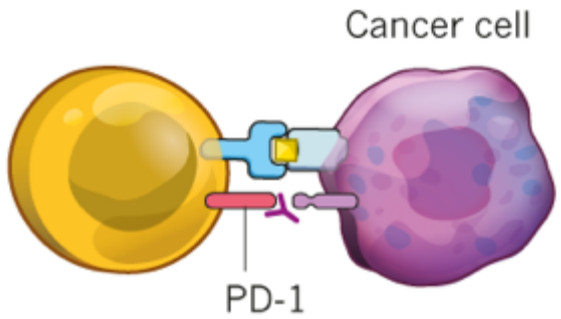



## Non-small cell lung cancer



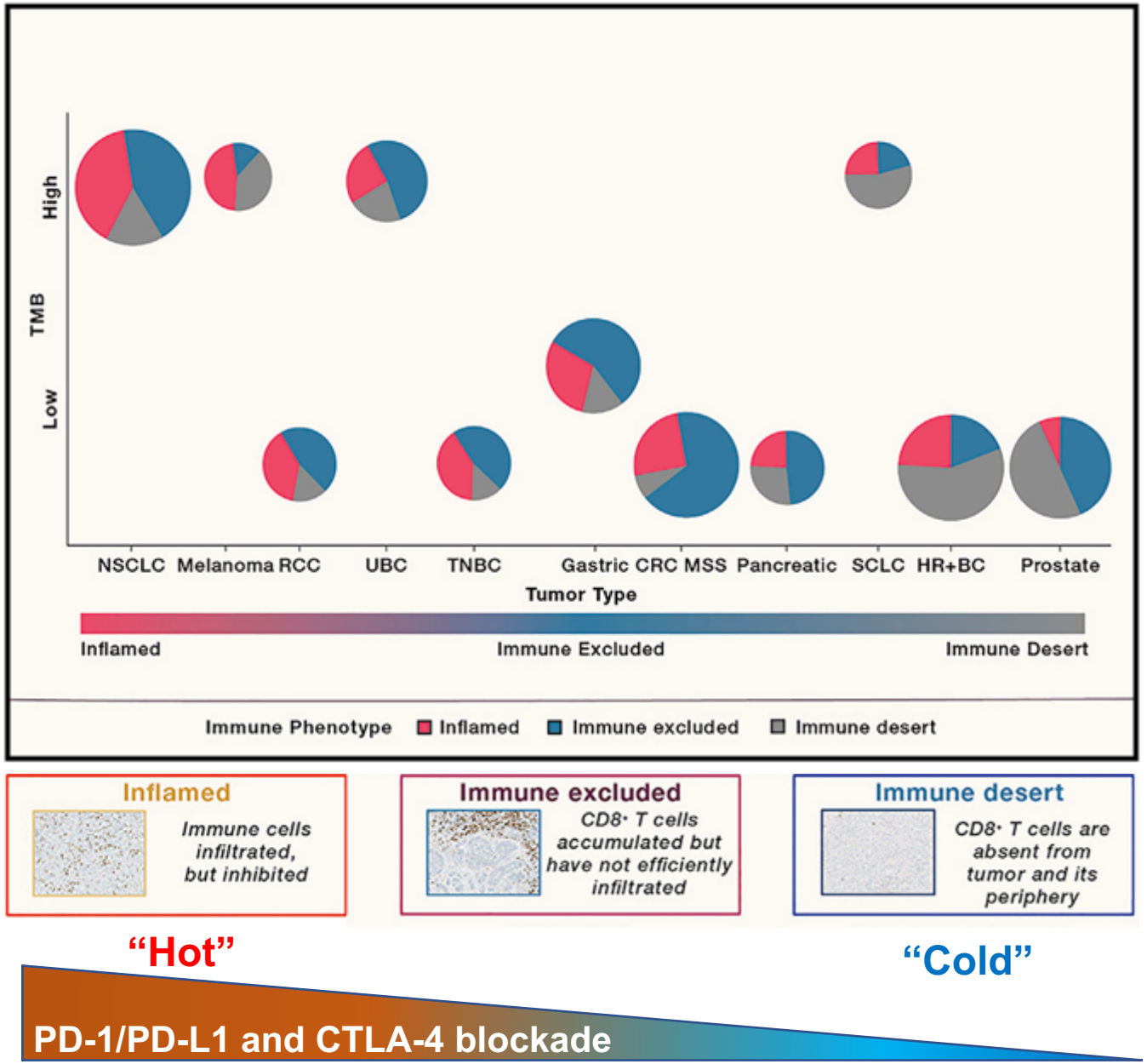

Hellmann et al NEJM 2018




Ledford et al Nature 2018

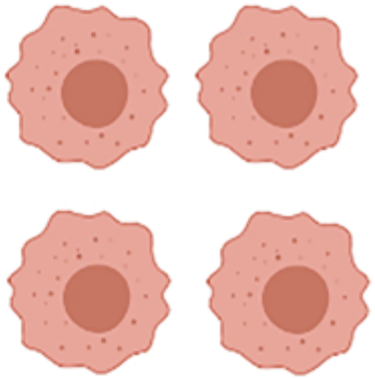
# Only subset of immunologically “Hot” tumor types responsive to immunotherapy




Hedge et al. Immunity 2019

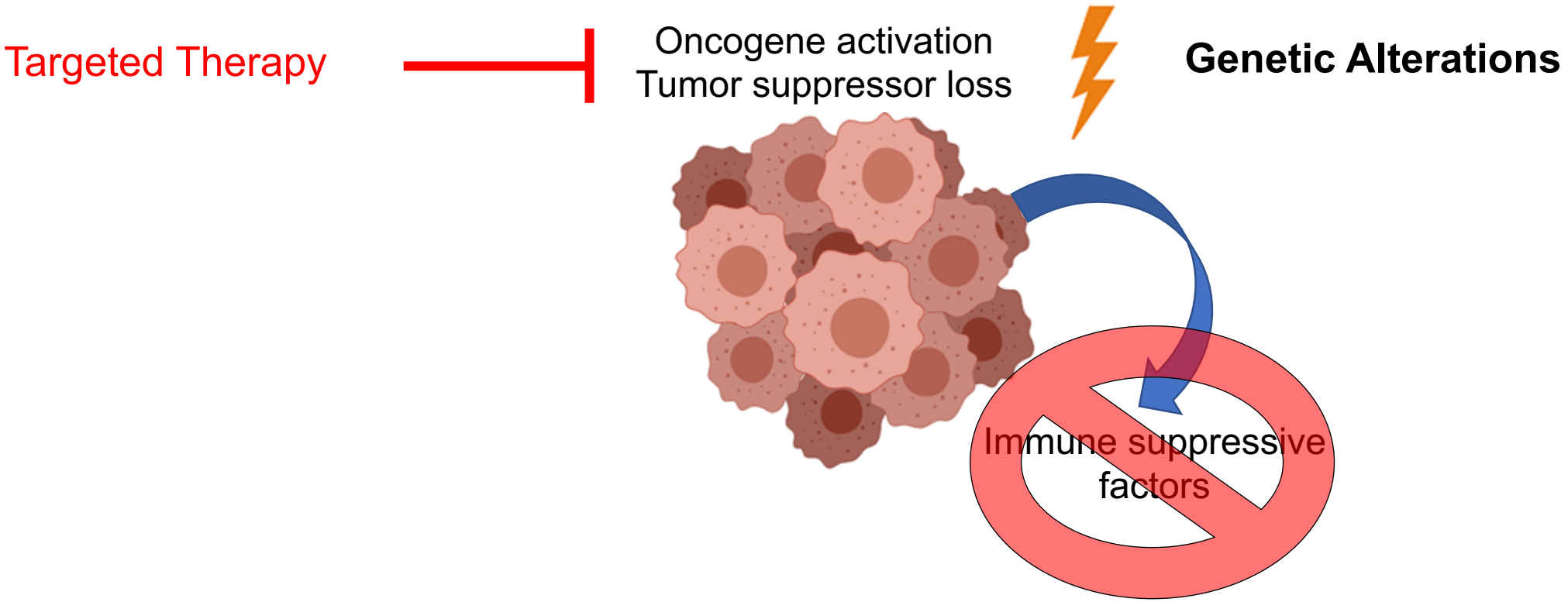
# Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

Oncogene activation
Tumor suppressor loss



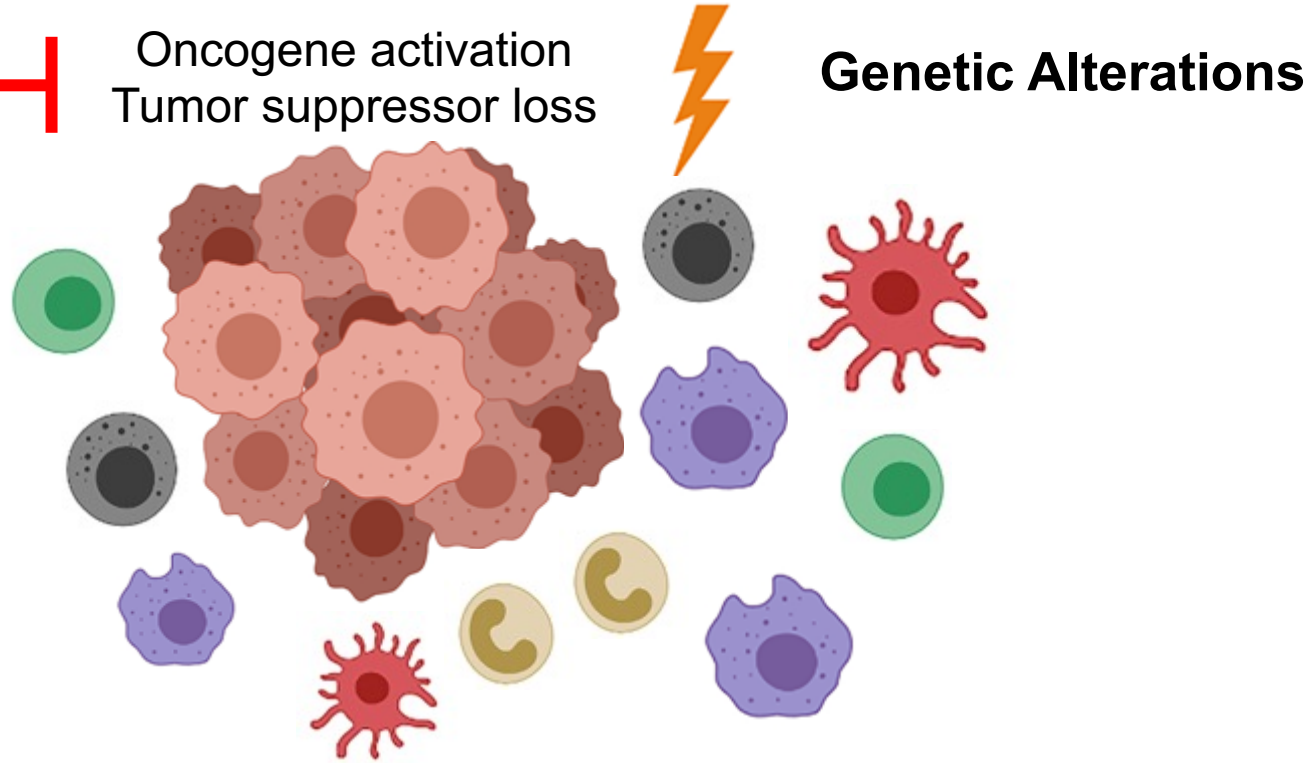
**Genetic Alterations**

# Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

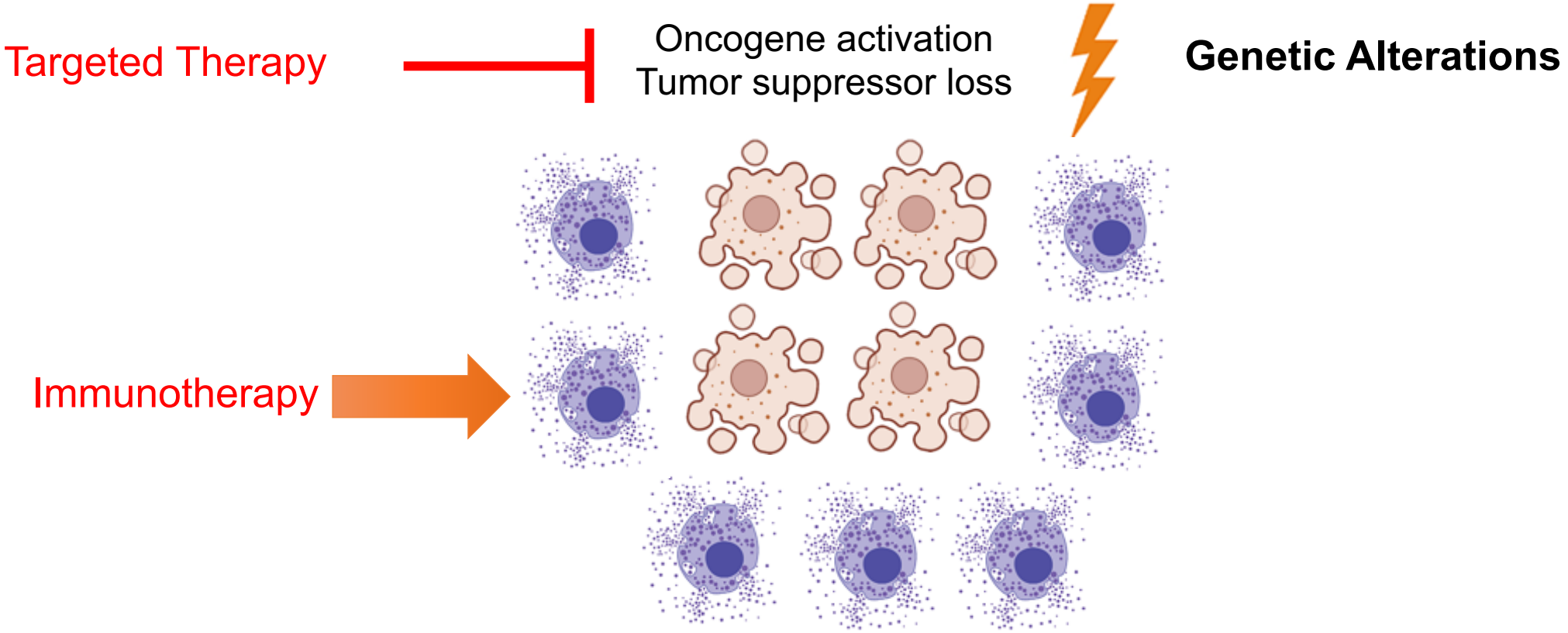


# Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

Targeted Therapy

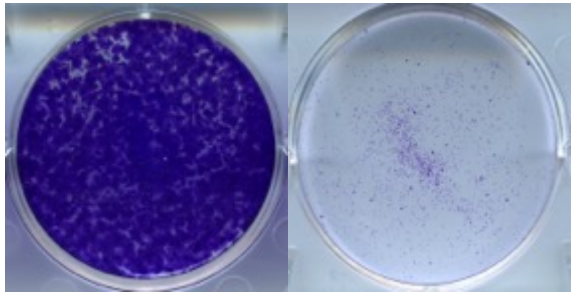


# Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

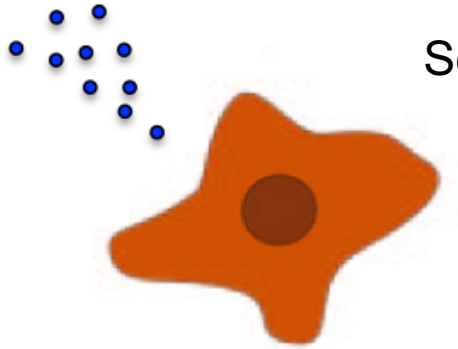


# **Cellular Senescence**: a two-component program linking intrinsic and extrinsic tumor suppression

⊙ **Stable cell cycle arrest**



⊙ **Modulation of the microenvironment**



Senescence-associated secretory phenotype (**SASP**)

Physiological stress response to damage

- *Telomere shortening (replicative exhaustion)*
- *Genotoxic stress*
- *Oxidative stress*
- *Oncogene activation*

Potent activation of secreted factors:

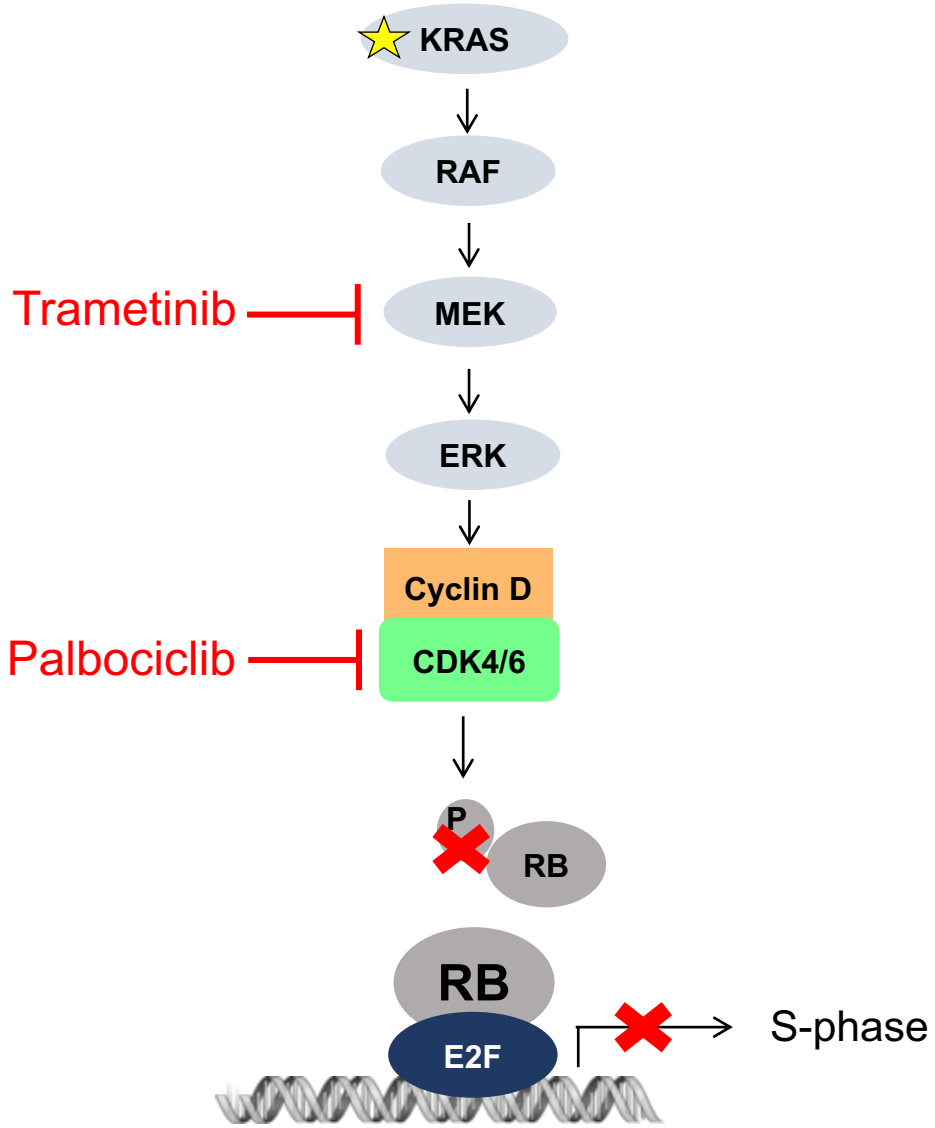
- *Pro-inflammatory cytokines/chemokines*
- *Growth and stemness factors*
- *Matrix metalloproteinases*
- *Angiogenic factors*

**p53 and RB pathway-regulated (gene repression)**

**NF-kB-regulated (gene activation)**

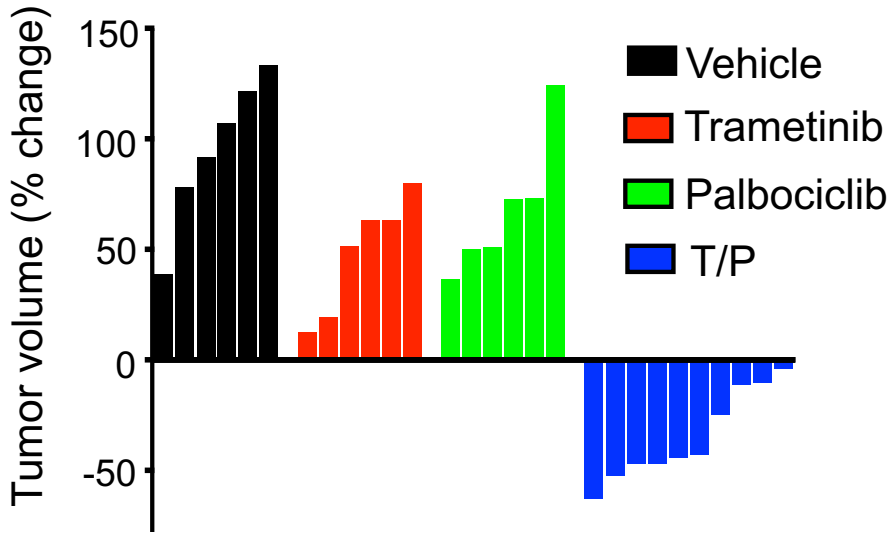
Hayflick, L. & Moorhead, P.S. Exp Cell Res 1961; Serrano, M. et al. Cell 1997; Xue, W. et al Nature 2007; Kang, T.W. et al. Nature 2011; Coppe, J.P. et al. PLoS Biol 2008; Chien, Y. et al. G&D 2011; Tasdemir, N. et al. Cancer Discov. 2016; Hoenicke & Zender Carcinogenesis 2012

# Senescence-inducing therapies for KRAS mutant cancers

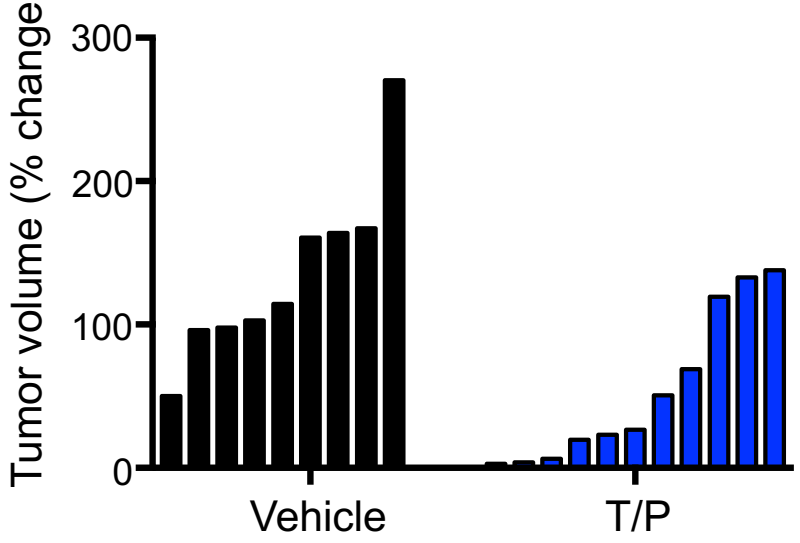



**RB-mediated senescence**

KRAS-driven lung cancer GEMMs

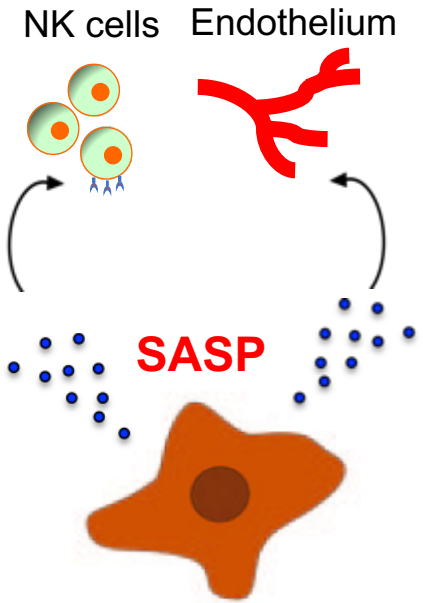



KRAS-driven pancreas cancer GEMMs

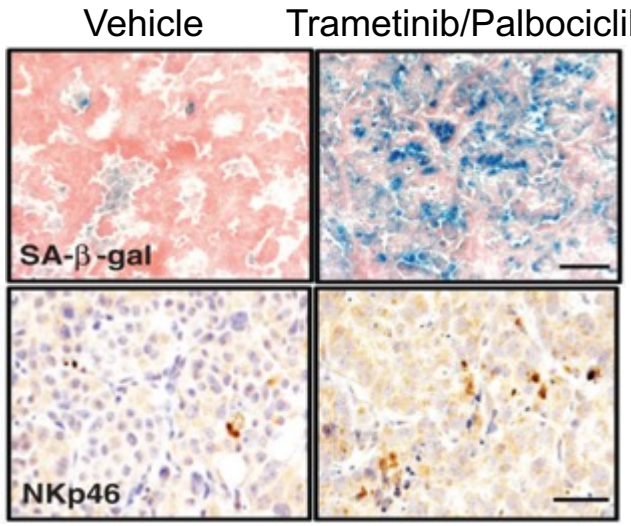


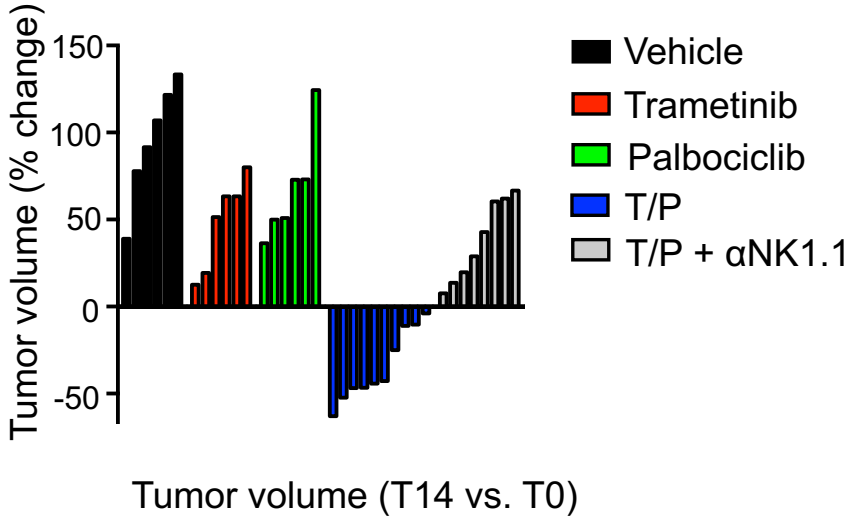

Ruscetti et al. Science 2018; Ruscetti et al. Cell 2020

# Therapy-induced senescence mediates divergent immune responses in different tissues



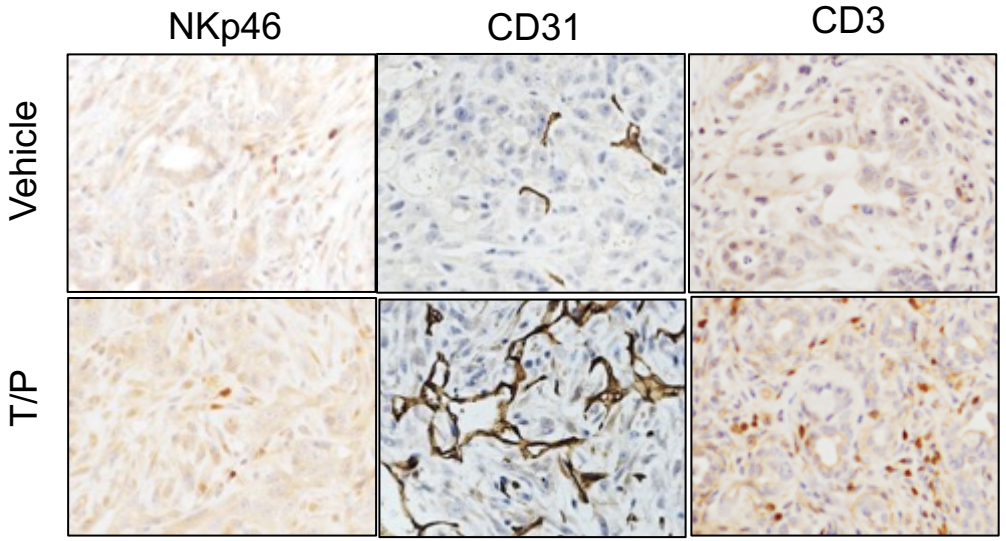

## KRAS-driven lung cancer

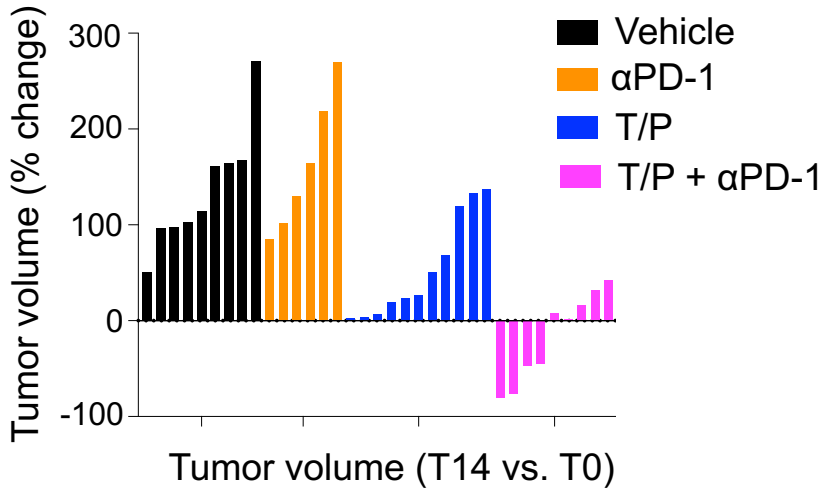



Ruscetti et al. Science 2018

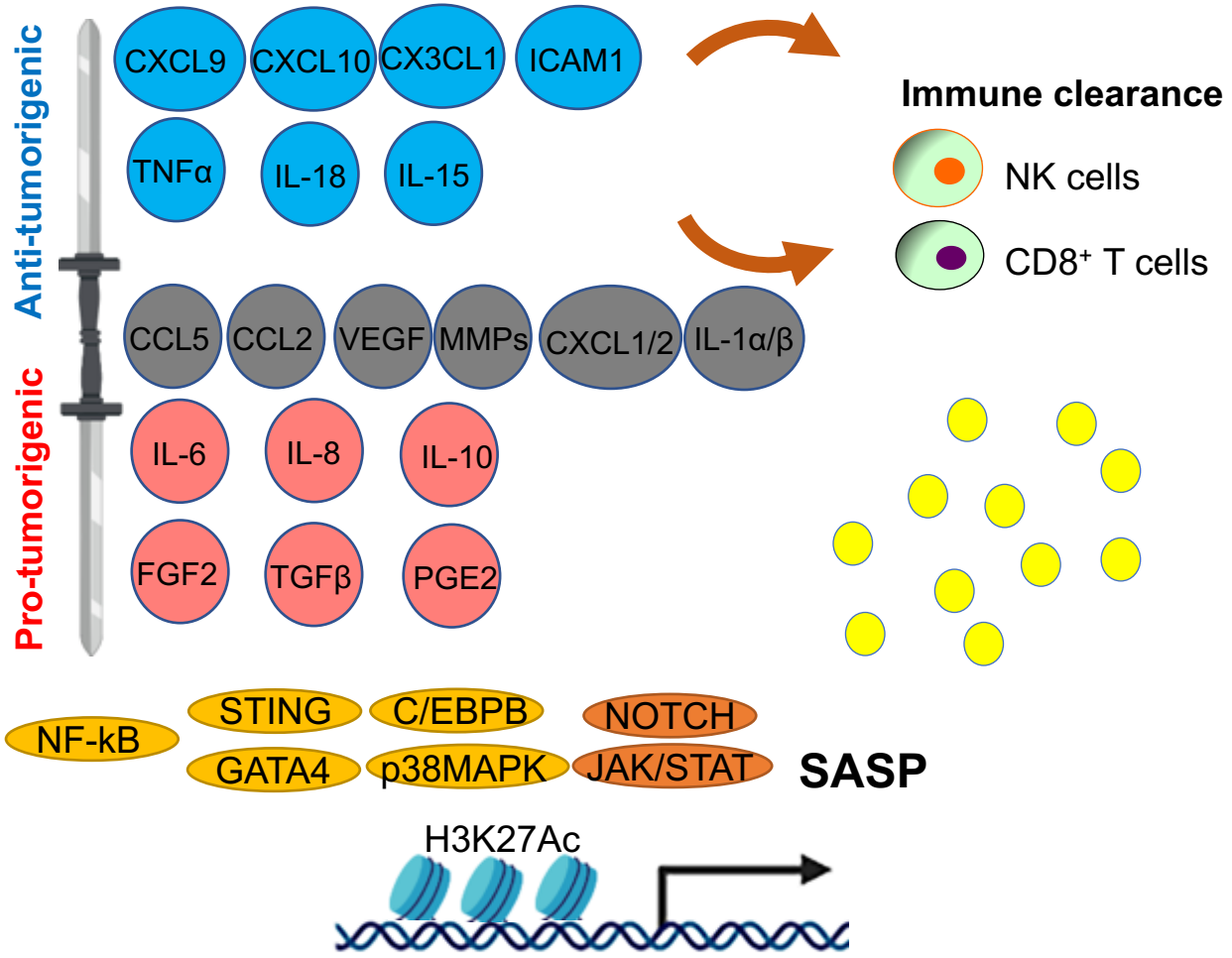
## KRAS-driven pancreas cancer

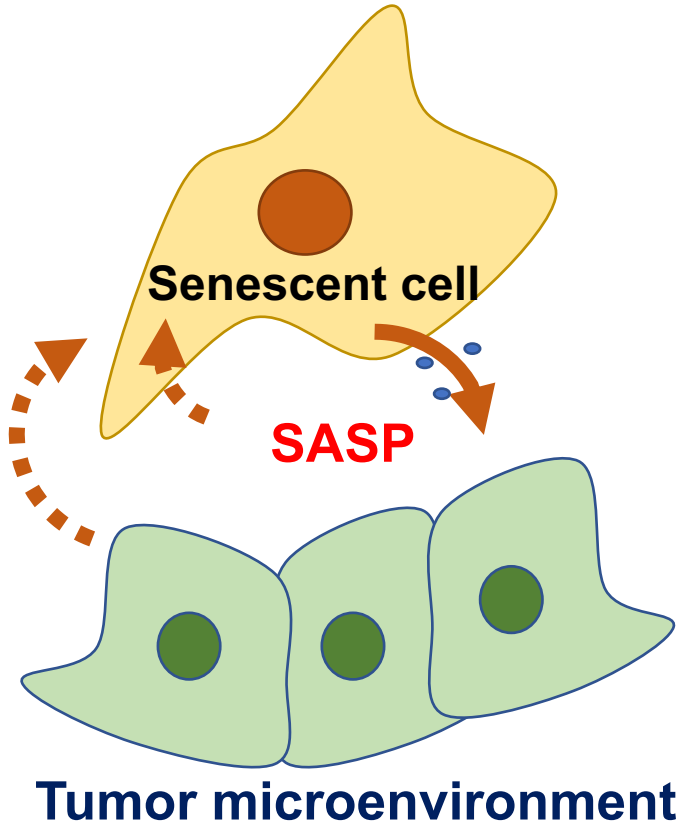



Ruscetti et al. Cell 2020

# SASP regulation in cancer: complexity and context-dependency

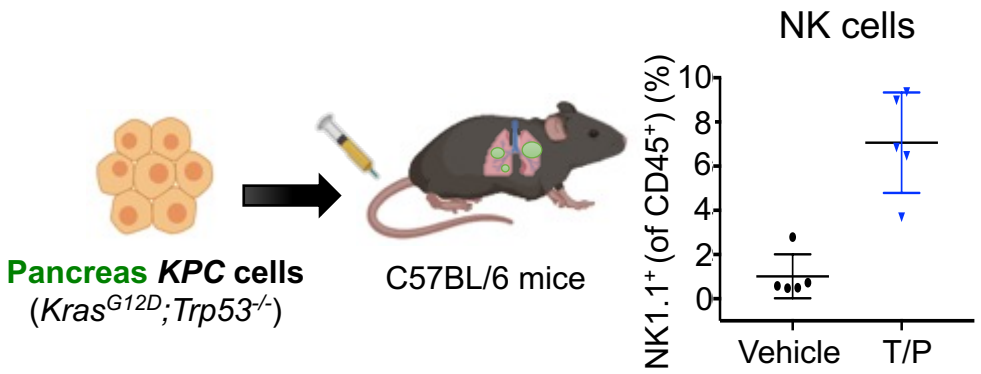


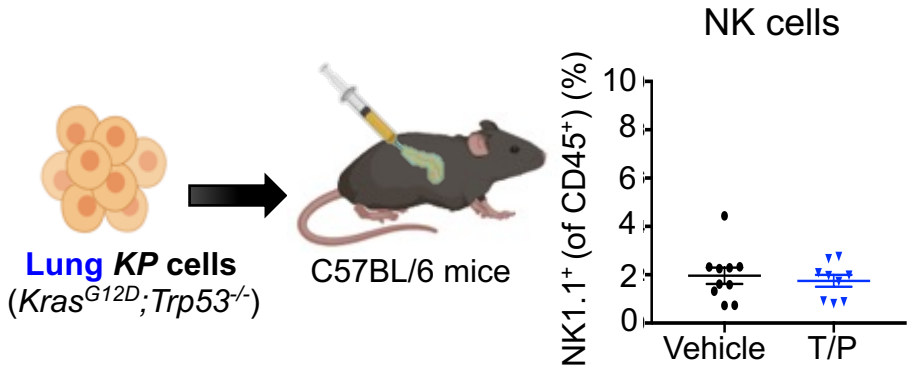

- **Which SASP factors are important for anti-tumor immune responses?**
- **How is the SASP transcriptionally regulated in different contexts?**
- **How does the resident microenvironment affect senescence and its impact on the immune system?**

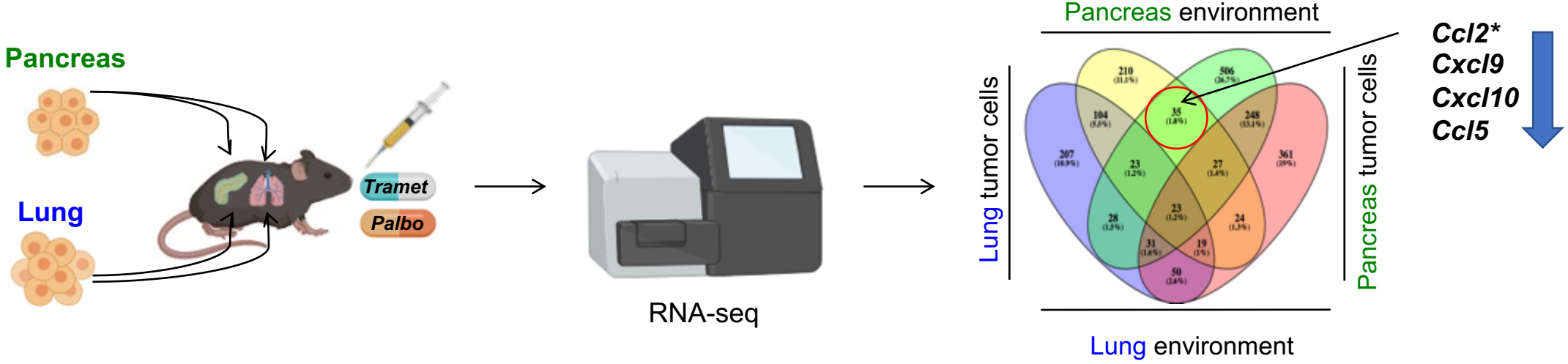
# Uncovering tissue-specific regulation of SASP-mediated immunity in pancreas cancer

**Pancreas** tumor cells in **lung** environment

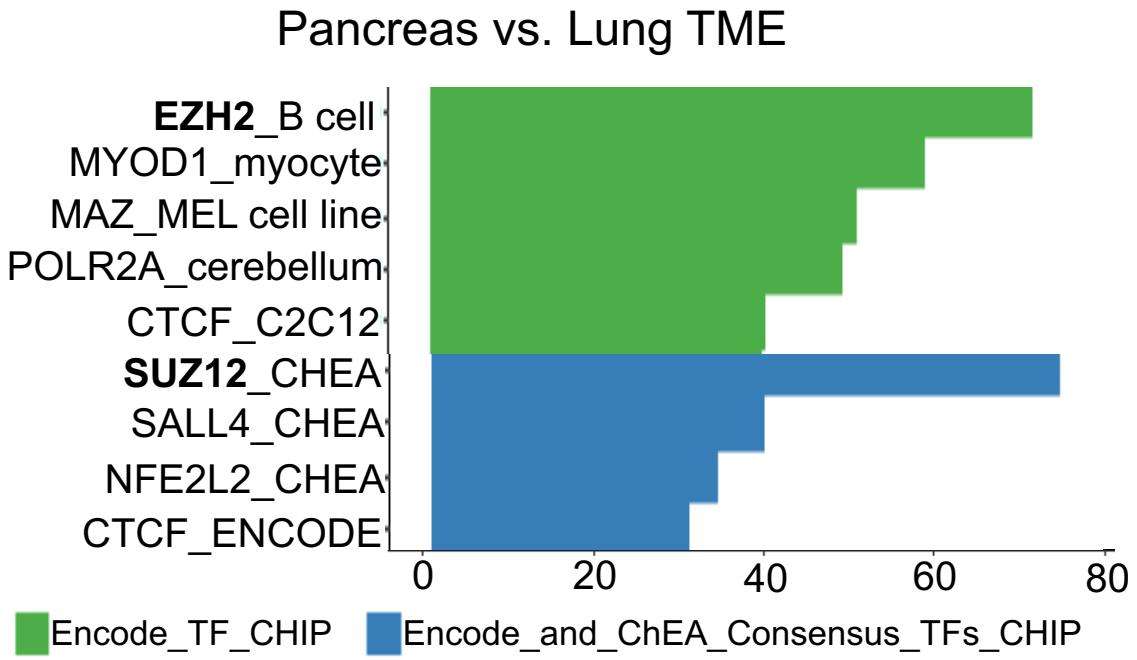


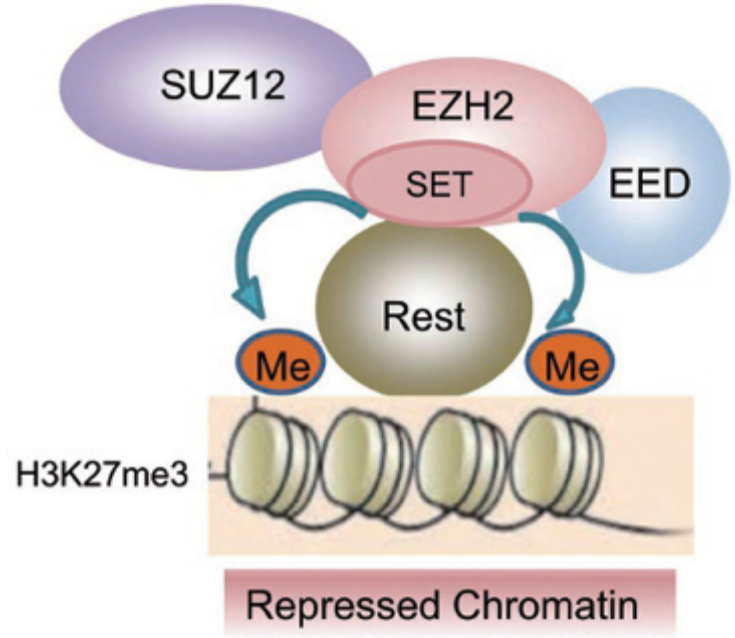

**Lung** tumor cells in **pancreas** environment

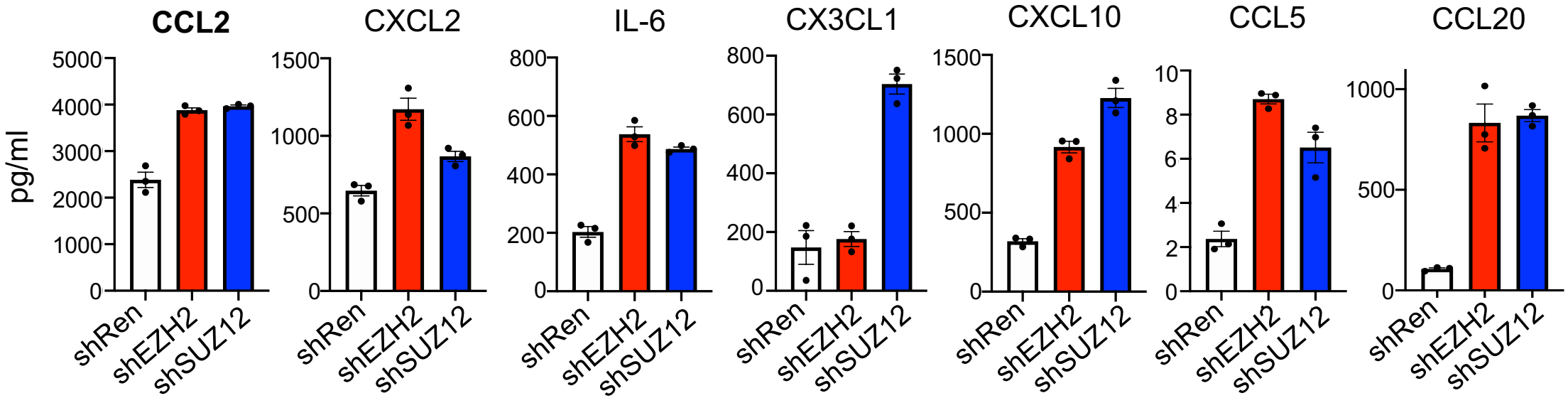


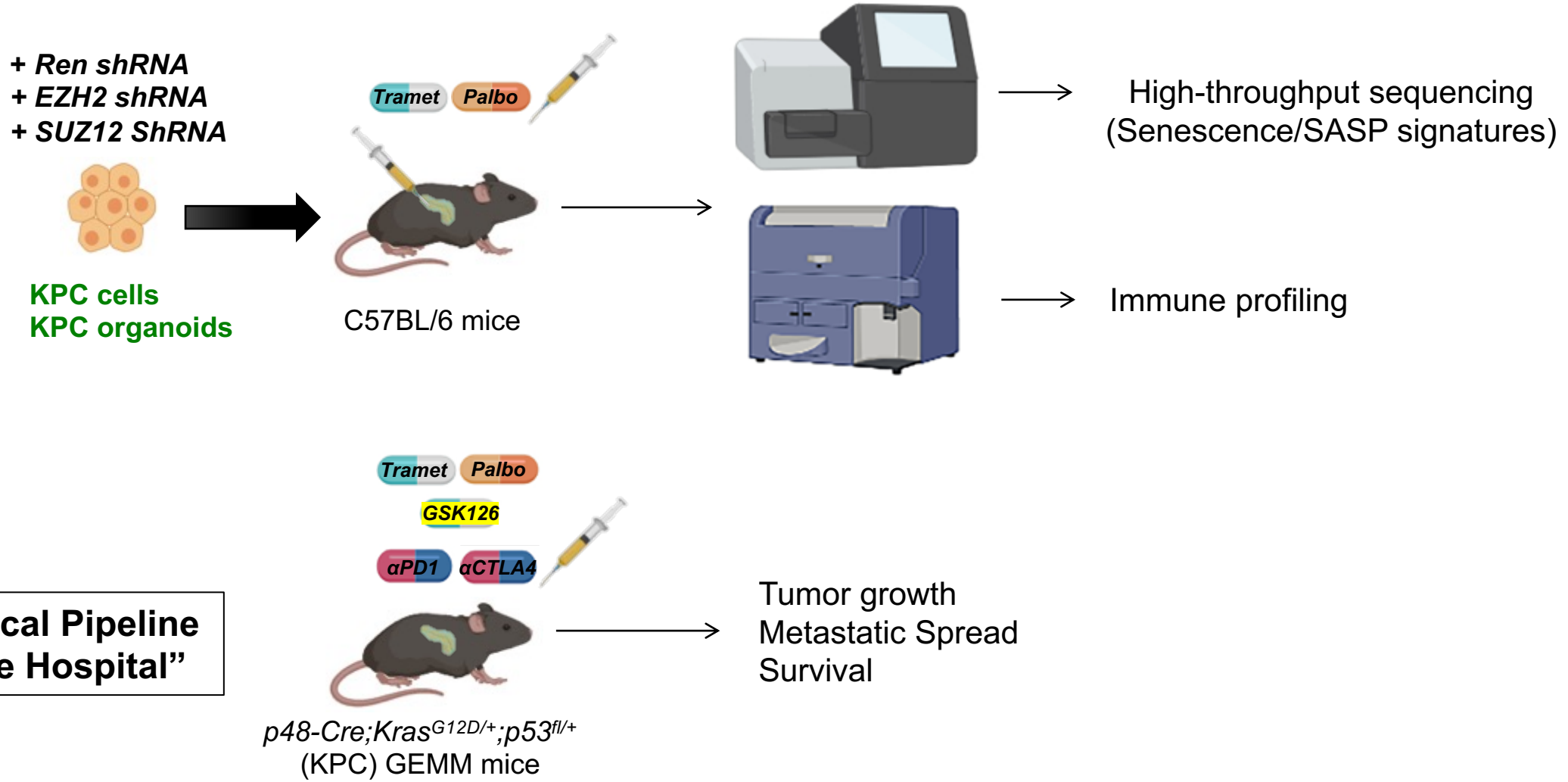
# EZH2 and SUZ12 are chromatin regulators that suppress SASP



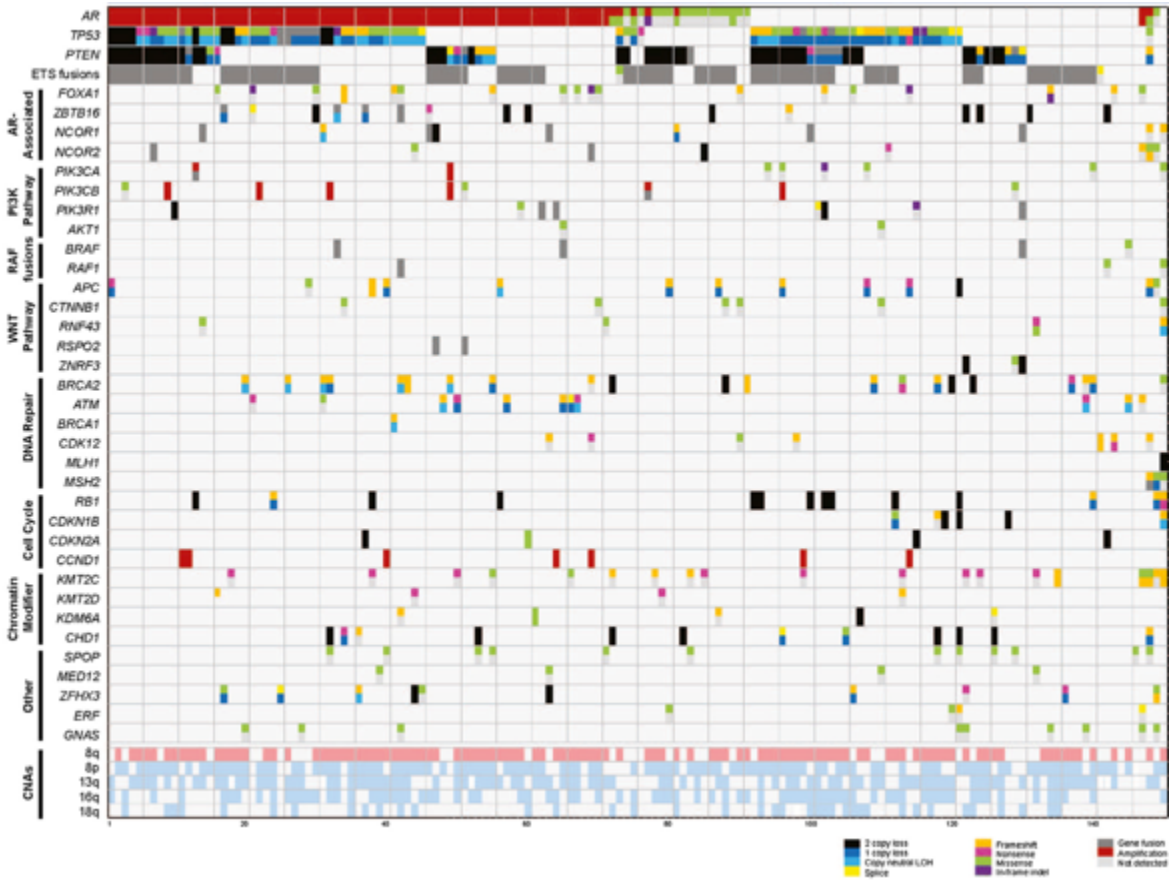
# Potentiating Immunotherapy in Pancreas Cancer Mouse Models




**Preclinical Pipeline**
**"Mouse Hospital"**

# Studying senescence and immune surveillance bypass in other genetic contexts and “cold” tumor types

## Prostate cancer




Androgen receptor (AR) pathway

PI3K pathway

WNT pathway

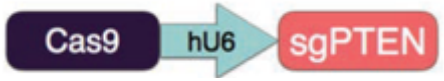
DNA repair

Chromatin modifiers

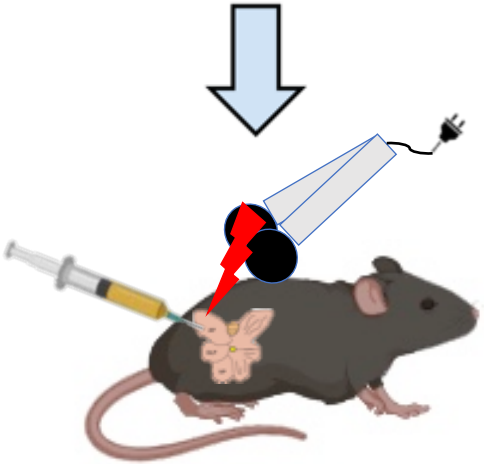
## Modeling prostate cancer in mice using *in vivo* electroporation


*Transposon Vector*

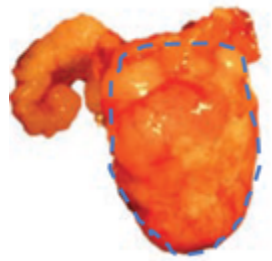

*Transposase*




*CRISPR/Cas9 Vector*



WT C57BL/6



**EPO-GEMMs**

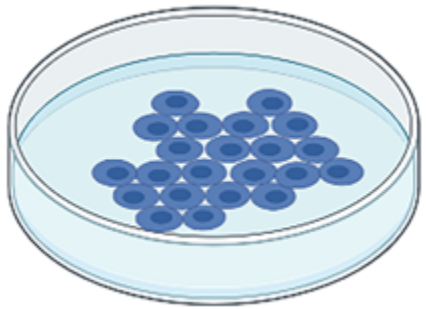
Robinson et al Cell 2015

Leibold*, Ruscetti* et al Cancer Discovery 2020

# Pipeline to identify and validate senescence-inducing compounds in tumor and genotype-specific manner

***In vitro***

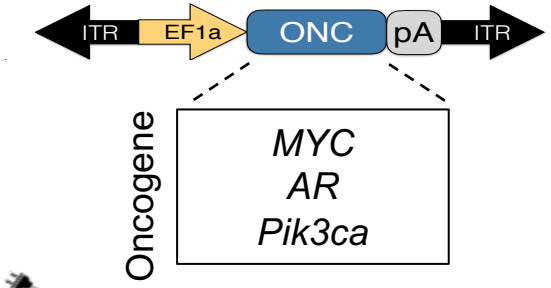
NF-KB reporter (SASP)
p16 reporter (senescence)

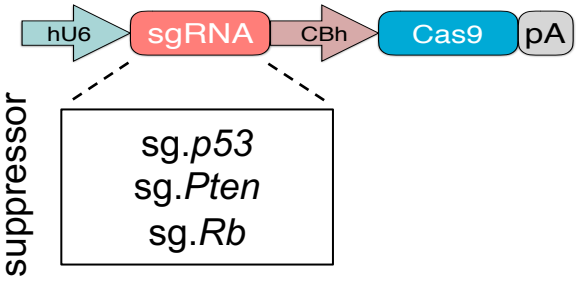


**Murine tumor cells with different genetic backgrounds**

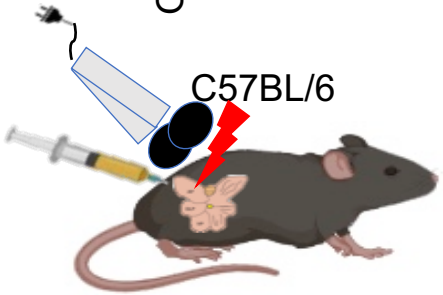
**Chemical Library Screens**

***In vivo***



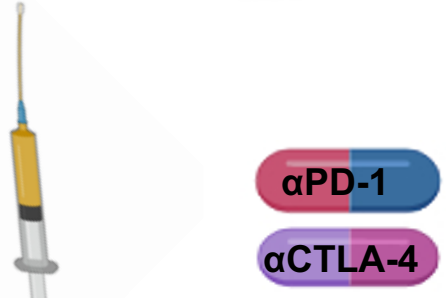

**Genetics**






**Immune background**


Senescence-inducing therapies




Immunotherapies

**Therapeutic Interventions**

**EPO-GEMM platform**

# Acknowledgements

**Ruscetti Lab**
Kat Murphy
Yvette Lopez
Loretah Chibaya
Megan Fowler (Rotation student)

**Julie Zhu (Bioinformatics Core)**
Haibo Liu

**Mike Lee (PSB)**

**Scott Lowe (MSKCC)**
John P. Morris IV
Ray Ho
Riccardo Mezzadra
Josef Leibold
Katerina Hatzi

**Charles Sherr (St. Jude)**

**MCCB Department**

**Funding**

NIH NATIONAL CANCER INSTITUTE

4R00CA241110 - 02